

The University of Chicago

THE ETIOLOGY OF GASTRIC
AND DUODENAL ULCER

Experimental Studies

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE
BIOLOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF SURGERY

1934

By

WARREN BOND MATTHEWS

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THE ETIOLOGY OF GASTRIC AND DUODENAL ULCER¹

EXPERIMENTAL STUDIES

WARREN B. MATTHEWS, M.S., M.D.

CHICAGO

From the Department of Surgery of
The University of Chicago

DURING the past 15 years there has been a renewed clinical interest in the problems presented by the etiology and pathogenesis of gastric ulcer and a large amount of excellent experimental work has been done which has greatly clarified already existing ideas concerning the significance of various factors in the cause of the disease. Perhaps the most important development during this period has been the successful production of chronic ulcer in the experimental animal. The early literature is replete with unsuccessful attempts to produce a chronic progressive lesion in the gastric or duodenal mucosa of dogs. This effort has served, however, to make evident the great capacity of the gastric mucosa of these animals to heal in the presence of the usual gastric content and after the most extensive mechanical and chemical traumas. Bolton (1913), Friedman and Hamburger (1914), Dragstedt and Vaughn (1924), Shapiro and Ivy (1926), Wolfer (1926), and others have produced chronic gastric ulcers in dogs by methods which are chiefly serviceable in determining the subsequent effect of these ulcers on the secretory and motor function of the stomach, but are of less significance in determining the cause of the spontaneous lesion. Exalto (1911) and especially Mann and his associates (1923) must be credited with being the first to develop methods which regularly lead to the production of chronic ulcers without the use of external destructive

¹ This work has been conducted under a grant from the Douglas Smith Foundation for Medical Research of The University of Chicago.

agencies. Largely as a result of the experiments of Mann and his associates in this country, the theory that ulcer is due primarily to the corrosive and digestant action of the pepsin-hydrochloric acid of the gastric juice has received a renewed emphasis and for the first time definite experimental support.

In this connection, however, and in spite of the evidence presented in this paper, it must be recognized that in dealing with the clinical problem many diverse agencies may produce an acute lesion in the human stomach. Such a lesion is not ordinarily under optimum environmental conditions for healing and we may list for subsequent examination those more obvious factors which might delay healing and induce chronicity. First, in otherwise healthy individuals it seems likely that the exposure of the acute lesion to the corrosive action of the gastric content would delay healing. In this connection the time of such exposure and the concentration of free acid and of pepsin in the gastric content should be of great significance. Second, comes the almost ceaseless motility of the stomach and especially of the pyloric region where chronic ulcers are so prone to develop. Here also the increased motility associated with pylorospasm and retention demands consideration. Third, the possible mechanical effect of coarse food particles pressed into an acute ulcer by the digestive motility of the stomach is of significance. In addition to these factors operative in healthy persons we must bear in mind a possible generalized decrease in the rate of healing or in the resistance of the gastric or duodenal mucosa to the digestant action of the gastric juice present in individuals rendered cachectic by anæmia, food deficiencies, endocrine disturbances, etc., through local vascular disease or thrombosis of the gastric blood vessels, decrease in the amount of gastric mucus, etc. Since chronic gastric ulcer is predominantly a disease of young and otherwise healthy adults, it seems improbable that these latter factors play any large rôle in the disease.

The present experiments were designed to determine in so far as possible the rôle of the chemical action of the gastric juice in the cause of ulcer and its relation to chronicity.

Interest in this problem has centered about the pepsin and hydrochloric acid rather than other constituents of the juice because of their great capacity to hydrolyze proteins. The question has been raised, "Why does the stomach not digest itself?" It has been commonly assumed that the mucosa lining the gastric wall has some specific resistance to such digestion not possessed by other living tissues and entirely absent in dead protein. An attempt was made by Dragstedt and Vaughn (1924) to secure experimental evidence regarding the resistance of various tissues to gastric digestion. In their experiments, large windows were produced in the stomach of dogs and into these defects were carefully sutured segments of duodenum, jejunum, ileum, colon, and such organs as spleen and kidney. In no case were these tissues digested away. The exposed surfaces of the spleen and kidney were soon covered by a layer of newly formed gastric mucosa while the mucosa of the duodenal and intestinal implants remained entirely normal for periods of at least 9 months. It is thus quite evident that there exists a widespread resistance to the digestant action of the normal gastric content on the part of tissues and organs whose blood supply is not interfered with. It should be emphasized that this experiment yields data only on the resistance of the tissues to the normal gastric content but not to pure gastric juice.

The experience of innumerable physicians during the past 50 years has established the fact that the free hydrochloric acid in the gastric content aspirated 1 hour after the ingestion of an Ewald meal varies between 30 and 60 clinical units in the case of normal individuals. Data obtained by the method of fractional gastric analysis advocated by Reh-fuss and his associates have in general confirmed this belief. On the other hand, it has been equally well established that the concentration of free acid in pure gastric juice, such as may be obtained from isolated portions of the stomach as in the experiments of Heidenhain and Pawlow, is much greater than this. The average free hydrochloric acid in the uncontaminated gastric secretion yielded by the completely isolated dog's stomach in the

TABLE I.—INTESTINAL ULCER AFTER IMPLANTATION OF STOMACH POUCHES

The incidence of chronic ulcer in the intestine following the implantation of stomach pouches (experimental diverticulum ulcers). Pawlow pouches were used in all cases except Dogs 5 and 6, in which Heidenhain pouches were employed

Dog No.	Size of pouch	Part of intestine used	Length of experiment	Fate of animal	Description of ulcer	Condition of animal at death
1	Small	Ileum	80 days	Sacrificed	2 x 3 cm.	Good. No weight loss
2	Small	Ileum	60 days	Died of distemper	2 x 1.5 cm. Subacute	Poor
3	Small	Ileum	77 days	Sacrificed	4 x 3 cm. Chronic	Fair. 20% weight loss
4	Small	Ileum	77 days	Sacrificed	2 x 3 cm. Chronic	Fair. 15% weight loss
5	Small	Ileum	34 days	Peritonitis	4 cm. diameter, 2 cm. deep. Perforated	Good. No weight loss
6	Small	Ileum	91 days	Sacrificed	1.5 cm. diameter, 0.5 cm. deep. Chronic	Poor
7	Large	Jejunum	29 days	Peritonitis	Size half hen egg. Perforated	Poor
8	Large	Jejunum	51 days	Hæmorrhage	4 cm. wide, 4 cm. deep	Good. 10% weight loss
9	Large	Jejunum	92 days	Intussusception	No ulcer	Very poor
10	Large	Jejunum	86 days	Peritonitis	Extensive destruction intestinal wall	Good. No weight loss
11	Large	Jejunum	24 days	Accidentally killed	3 cm. diameter. Chronic	Good. No weight loss
12	Large	Jejunum	83 days	Peritonitis	Crater, size goose-egg	Very poor
13	Large	Jejunum	98 days	Sacrificed	4 cm. wide, 4 cm. deep. Crater	Poor
14	Large	Jejunum	103 days	Evisceration	No ulcer	Good. No weight loss
15	Large	Jejunum	93 days	Not killed	2 cm. diameter. Chronic	Good. No weight loss
16	Large	Jejunum	22 days	Peritonitis	2 x 4 cm. Perforated	Fair. 10% weight loss
17	Large	Jejunum	52 days	Peritonitis	4 x 3 x 3 cm. Chronic	Poor. 30% weight loss
18	Large	Jejunum	14 days	Peritonitis	1.5 cm. diameter	Good. No weight loss
19	Large	Jejunum	160 days	Peritonitis	Chronic 5 x 4 cm.	Poor. 50% weight loss

experiments of Dragstedt and Ellis (1930) varied between 0.35 and 0.49 per cent, the latter figure being by far the more common finding. These values correspond to approximately 100 and 135 clinical units. A similar figure (0.40 to 0.50 per cent free hydrochloric acid) has been given for pure unmixed gastric juice in man (Carlson, 1923).

If it be conceded that it has been difficult or impossible to demonstrate any deterrent effect on the healing of acute lesions in the stomach of experimental animals due to the corrosive chemical action of the normal gastric content, the question naturally arises, may not *pure gastric juice* with its *higher free acid* exert such an effect? As a corollary to this we may perhaps profitably inquire into the factors which normally reduce the acidity of pure juice to that of the normal gastric content. Those that come readily to mind may be listed as the neutralizing effect of food and swallowed saliva, mucus secreted in the œsophagus, fundus, and particularly in the pyloric antrum of the stomach, fixed base secreted chiefly in the pyloric antrum, and regurgitated alkaline juices from the upper duodenum. Does a defect in this neutralizing mechanism or any part of it account for the fact that a majority of patients with duodenal or gastric ulcer have a gastric content of higher than normal acidity and one which approaches the acidity of pure juice?

THE PRODUCTION OF CHRONIC ULCER BY PURE GASTRIC JUICE

a. *Meckel's diverticulum ulcer*. Perhaps the most striking evidence to be obtained from human pathology in support of the view that the chemical action of gastric juice may produce a chronic ulcer is the occurrence of such a lesion in the mucosa of the ileum adjacent to the entrance of Meckel's diverticulum. Aschner and Karelitz (1930) and Lindau and Wulff (1931) have summarized the clinical literature bearing on this problem and have pointed out that in those cases in which ulcer has been present, islands of heterotopic gastric mucosa, histologically similar to that in the fundus of the stomach, have been almost invariably found in the diverticulum. Additional proof that this heterotopic gastric

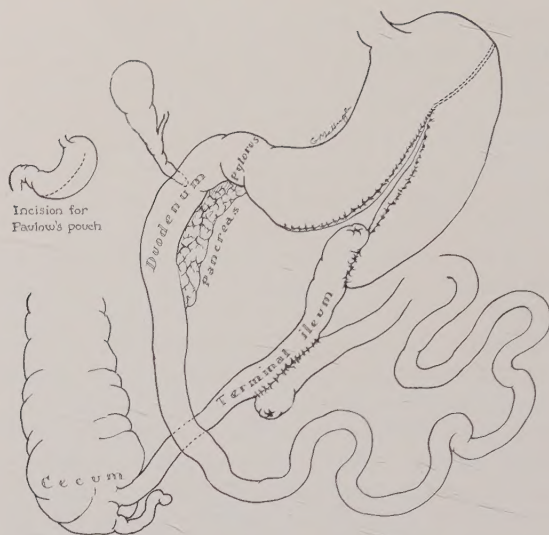


Fig. 1. Diagram showing the method of implantation of the Pawlow accessory stomach into the ileum for the experimental production of "Meckel's diverticulum ulcer."

mucosa is functional has been cited in the occasional persistence of the vitelline duct as a fistula opening at the umbilicus and discharging an acid proteolytic secretion capable of corroding the skin. Both pepsin and free hydrochloric acid have been detected in this secretion (Lindau and Wulff), and the amount of secretion has been found to increase greatly when food is taken in the stomach. This is undoubtedly due to the stimulating effect of gastrin bodies discharged into the general circulation during gastric digestion since secretory nerves to these islands of gastric tissue have not been found. In this connection it should be noted that Ivy and Farrell (1925) autotransplanted small pouches of the fundic portion of the stomach subcutaneously in dogs and observed that following a meal the transplant secreted acid. All nervous connections between the transplant and the main stomach had been severed. The Meckel's diverticulum ulcer invariably occurs adjacent to the heterotopic gastric mucosa but always involves only the mucosa of the ileum. This fact suggests that the ileal mucosa is more susceptible to the chemical action of gastric juice than is gastric mucosa, a point to be elaborated upon later in the discussion. The ulcer appears early in life, usually within

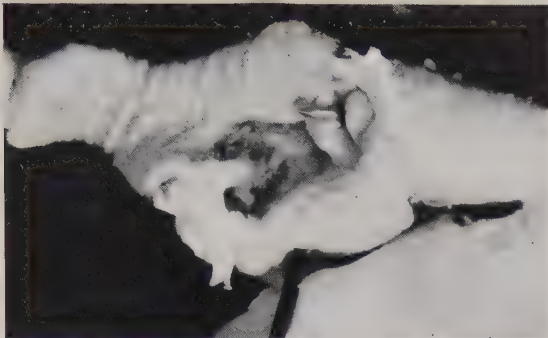


Fig. 2. "Experimental Meckel's diverticulum ulcer" of the ileum in Dog 4, Table I. The gastric pouch is to the right of the picture. A probe protrudes from the opening of this pouch in the ileum. Note the large size of the ulcer and its proximity to the gastric mucosa.

the first 18 months, and repeated hæmorrhages and occasionally perforation occur.

Because of the theoretical importance of these clinical observations and the possibility that the mucous membrane of the dog might behave somewhat differently, we have at the suggestion of Dr. D. B. Phemister performed experiments designed to imitate so far as possible the situation found in Meckel's diverticulum ulcer.¹

Experimental procedure. Healthy dogs were secured and all operations were performed under complete ether anæsthesia with the usual aseptic precautions. A small Pawlow pouch, 2 by 3 by 8 centimeters, was made from the greater curvature of the stomach in the region of the fundus. A segment of ileum, about 30 cubic centimeters proximal to the ileocæcal valve, was then selected, the intestine divided, and the distal ileum united to the open end of the Pawlow pouch. The continuity of the intestine was then re-established by anastomosing the proximal ileum to the distal intestine about 15 centimeters below its attachment to the gastric pouch (Fig. 1). Particular care was taken not to bruise the tissue or to damage its blood supply. No clamps were applied and only chromic catgut (No. 00) was used for the anastomoses. In a few of the experiments a pouch, the nervous connections of which had been first severed (Heidenhain pouch), was

¹A preliminary report of this work was published in the Proceedings of the Society for Experimental Biology and Medicine, 1931, xxviii, 960.

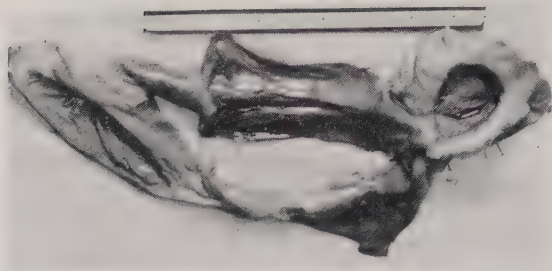


Fig. 3. "Experimental Meckel's diverticulum ulcer" in the jejunum of Dog 8, Table I. The opened gastric pouch is above and to the left of the ulcer. Note the large size of this ulcer, its sharp margins, and the persistence of a narrow zone of jejunal mucosa between the ulcer and the gastric mucosa.

used for anastomosis with the lower intestine. After the results of these experiments were determined, the operations were repeated on other animals, but in this case a very large Pawlow pouch was made (approximately $\frac{1}{2}$ to $\frac{2}{3}$ of the entire stomach) and its open end anastomosed to different regions of the jejunum, in some cases as far proximal as the ligament of Treitz.

The animals recovered from the operations promptly. They were given saline intravenously but nothing by mouth for the first 4 to 5 days. Following this they were given the regular stock diet of the laboratory, consisting of ground meat, bread, carrots, and other vegetables and were fed once a day. Those that survived for as long as 2 to 3 months were usually subjected to a second laparotomy and the condition of the intestine determined by inspection.

The results of the experiments are summarized in Table I. Of the 19 animals operated upon, 8 died of peritonitis following perforation of an intestinal ulcer, 6 were sacrificed when they became markedly cachectic, while the 5 remaining were in excellent condition at the time they were etherized for examination. Seventeen of the 19 animals had developed large typical chronic ulcers in the intestine adjacent to the anastomosis with the gastric pouch. In the cases in which the isolated gastric pouch was implanted into the ileum (6 dogs), chronic ulcers appeared in all, an incidence of 100 per cent, whereas when the implantation was made in the jejunum even though a much larger pouch was used, the

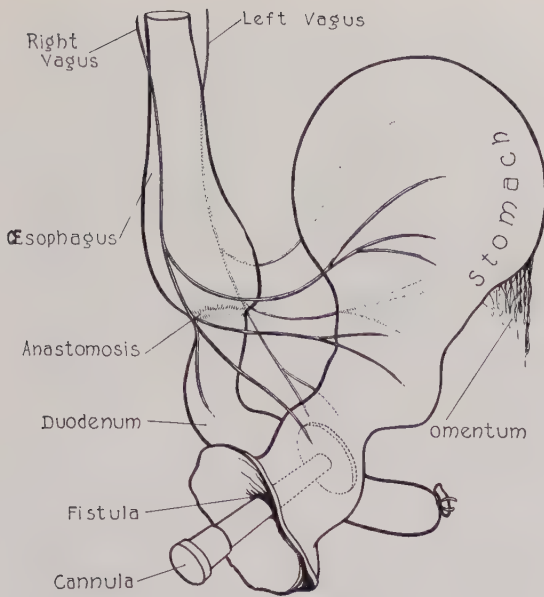


Fig. 4. Diagram showing the method of preparation of the isolated stomach with vagus innervation intact. (From Dragstedt and Ellis, *Am. J. Physiol.*, 1930, xciii, 407.)

incidence of ulcer was less (11 ulcers in 13 animals operated upon or 85 per cent). In many cases (roughly $\frac{1}{3}$ of the total) the ulcer seemed to have little deleterious effect upon the general condition of the animal until a sudden perforation or exploratory laparotomy revealed its presence. The shortest time elapsing between the date of operation and discovery of the ulcer was 14 days, the longest 160 days, and the average, 67 days.

It is significant that the ulcers always developed in the intestinal wall adjacent to the line of union with the gastric mucosa (Figs. 2 and 3). In most cases a narrow line of intestinal mucosa was visible between the ulcer and the nearest gastric mucosa. The latter was never involved. The ulcers presented the same clean, punched-out, "digested" appearance characteristic of the lesion in man. Their size was often enormous, and in several a crater large enough to contain an average size hen's egg was present. The floor of such an ulcer was composed of hyperplastic fibrous connective tissue, the remains of an inflamed, indurated omentum, loops of neighboring intestine, mesentery, and in some cases organs such as the pancreas or liver. All

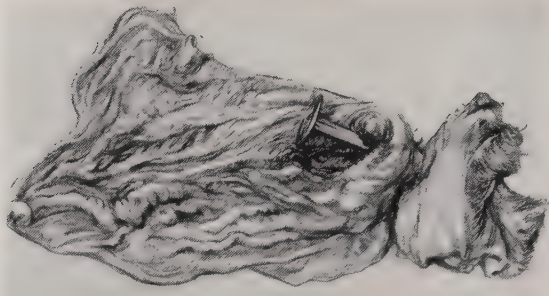


Fig. 5. Drawing showing the formation of a large, chronic, progressive ulcer in the isolated stomach.

were combined to form a large indurated inflammatory mass, requiring very careful dissection.

Microscopic examination of the intestinal mucosa in the immediate neighborhood of the ulcer presented evidence of inflammation, such as round cell infiltration, suggestive of the so called Konjetzny gastritis.

The successful production of chronic perforating ulcer in the ileum of dogs under conditions resembling those in the Meckel's diverticulum ulcer in man indicates that the susceptibility of the two species to the development of this disease may not be greatly different under comparable conditions. It seems probable that we may disregard the factor of operative trauma as of any great significance in the genesis of the experimental ulcer. In a few cases the region of the anastomoses was examined at a second laparotomy from 7 to 14 days after the first operation, and in each case healing was complete or progressing satisfactorily without evidence of ulcer. Furthermore, the almost invariable persistence of a strip of intestinal mucosa between the ulcer and the line of anastomosis suggests that the probable vascular damage to the intestine as a result of incision and subsequent suture was not of paramount importance in the ulcer formation. In man, of course, there can be no question of trauma or vascular injury, and we must attribute the ulcer to the destructive effect of the gastric juice. In both cases it is probably of considerable importance that the gastric juice enters an ileum empty of food or secretion and consequently its free acid is little reduced. Secretion of gastric juice in the

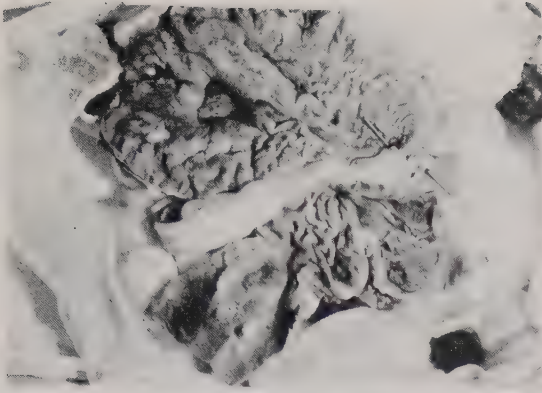


Fig. 6. Chronic perforating ulcer occurring spontaneously in a very large Pawlow pouch. The mucosa of the lesser curvature or *Magenstrasse* shown below to the right and that of the first part of the duodenum to the left are normal.

Pawlow pouch begins with the entrance of food in the mouth as a result of reflex stimulation of secretory nerves in the vagi and accordingly its pepsin hydrochloric acid comes in contact with the mucosa of the ileum long before food reaches this level and could possibly exert a neutralizing effect. Even in the experiments with the Heidenhain pouches and in the clinical cases it is likely that the hormone stimulation of the gastric mucosa produces a secretion before food reaches the ileum. At all events the production of intestinal ulcers by implants of gastric mucosa, completely separated from all connections with the central nervous system, speaks volumes against the rather fanciful idea that the latter plays a rôle in the proximal cause of the lesions. As noted above the incidence of ulcer in the intestine was 100 per cent when the gastric pouch (with or without nerves) was implanted into the ileum but only 85 per cent when the implantation was made in the jejunum. This may be interpreted to indicate a greater resistance on the part of the jejunal mucosa or it may be due to the earlier appearance of the chyme and neutralizing secretions of the upper duodenum.

The absence of ulcer formation in segments of jejunum or ileum implanted into the stomach as in the experiments of Dragstedt and Vaughn (1924) and the uniform occurrence of such lesions in the intestine when segments of stomach are implanted as in the experiments described, are striking and, at



Fig. 7. Photograph showing extensive digestion of the mesentery following rupture of a chronic ulcer in a large Pawlow pouch permitting several hundred cubic centimeters of very acid gastric juice to escape into the peritoneal cavity.

first glance contradictory phenomena. The essential difference in the two experiments lies probably in the removal of the entire neutralizing mechanism in the latter case so that the intestinal mucosa is exposed to the acid pepsin concentration of *pure fundus secretion* whereas when the intestine is implanted into the stomach it is exposed only to the acid-pepsin concentration of the usual gastric content, i.e., after dilution and partial neutralization by the mechanisms suggested in the introduction.

b. *Occurrence of chronic perforating ulcer in the isolated stomach.* It is noteworthy in the experiments described in the preceding section that in no instance did ulcers appear in the gastric pouch, whereas in a very large proportion of cases, large, chronic, progressive ulcers developed in the mucosa of the ileum and jejunum. The operative trauma to the gastric mucosa was obviously greater and it must have been exposed to as high or a higher concentration of pepsin hydrochloric acid than the intestine. These facts suggest that the gastric mucosa does actually possess a greater resistance to the digestant action of pure gastric juice than is present in the mucosa of the intestine lower down. If pure, unneutralized gastric juice is able to produce a chronic ulcer in the stomach, it would appear that the

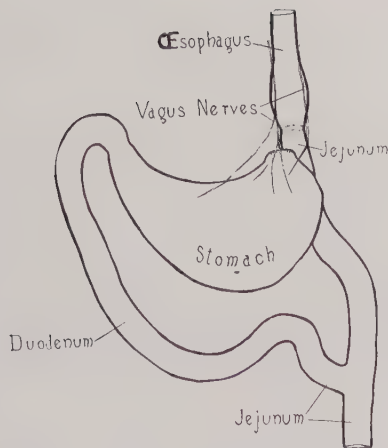


Fig. 8. Diagram showing the type of preparation used to determine the effect of gastric secretion in the stomach empty of food on the occurrence of ulceration of the intact gastric mucosa.

optimum conditions for such a lesion should exist in the so called isolated stomach. Frémont (1895) made a brief allusion to some experiments performed on dogs in which he had isolated the stomach, suturing the duodenum to the œsophagus and collecting the gastric secretion by means of a fistula. Inasmuch as he states that such a stomach to which the vagi have been cut secretes a fluid containing no acid and is non-digestive, we may question whether he actually secured a good preparation. Lim, Ivy, and McCarthy (1925), however, isolated the entire stomach of dogs, using the method described by Frémont, and Ivy has kept such animals alive for a number of years. Although the vagus nerves to these isolated stomachs have been cut they secrete a highly acid proteolytic juice. In no case has Ivy (1931) observed an ulcer in such a stomach. It should be noted, however, that in all these experiments the gastric juice has been permitted to flow away from the stomach by way of a fistula almost as soon as it is secreted so that there is at no time a prolonged contact of the active juice with the mucosa. It is likely that this fact is of decisive importance. L. R. Dragstedt and Ellis (1930) described a method for preparing an isolated stomach in the dog, leaving the vagus innervation intact and making a fistula with a metal cannula, by means of which it is

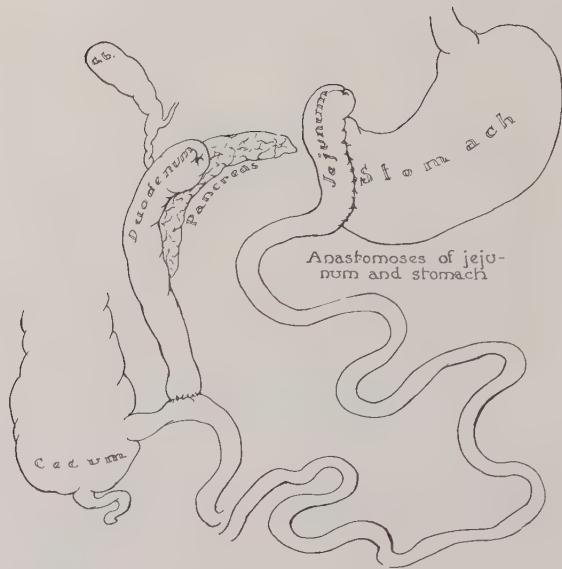


Fig. 9. Diagram showing the author's modification of the experiment of Mann for the production of jejunal ulcer by "surgical duodenal drainage." In spite of the resection of the pyloric antrum and the large anastomosis, chronic ulcers developed in 100 per cent of cases.

possible to retain pure gastric juice in the stomach at will (see Fig. 4). During the past 5 years a number of such animals have been kept in the laboratory. For the most part gastric juice has been permitted to flow out of the fistula into a collecting rubber bag so that to date the full advantage of the method for determining the effect of pure gastric juice on gastric mucosa has not been obtained. However, in one case a large typical chronic ulcer (see Fig. 5) was found in the isolated stomach. As will be noted from the illustration this lesion occurred close to the entrance of the cannula so that we cannot exclude this mechanical factor in the etiology. However, when such a cannula is placed in the normal intact stomach or intestine it has never produced such a defect.

c. *Occurrence of a chronic perforating ulcer in a Pawlow accessory stomach.* A small isolated accessory stomach made from the fundus, after the method of Pawlow, has been widely used in many physiological laboratories during the past 30 years for the study of the physiology of gastric secretion. To our knowledge no one has to date reported the

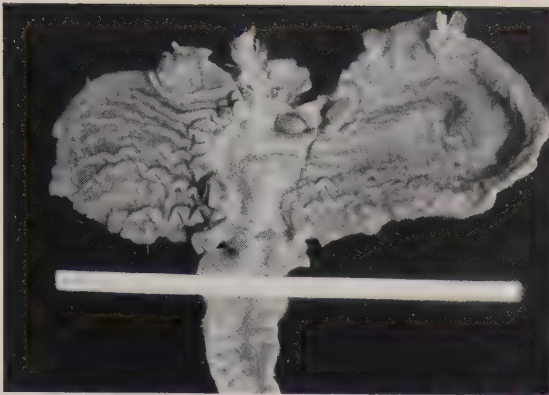


Fig. 10. Photograph showing the formation of a jejunal ulcer following the type of operation illustrated in Figure 9.

spontaneous occurrence of an ulcer in such a pouch. As noted in the preceding section, this may be due to the fact that the gastric juice is commonly promptly drained away by the fistula and so does not remain in contact with the gastric mucosa for any appreciable length of time. However, in 1917, L. R. Dragstedt tried to prepare Pawlow pouches in dogs in such a way that the gastric secretion should be retained in the pouch, by implanting the fistulous opening in the skin of the lateral abdominal wall, instead of on the ventral surface. Spontaneous ulcers did not occur in these pouches and acute lesions produced by silver nitrate seemed to heal as readily as in control dogs where the accessory stomach was continually drained. An examination of the data respecting the acidity of the gastric juice from these pouches, however, suggests an explanation for these negative results. The free hydrochloric acid varied between 0.00 and 0.109 per cent with an average of about 0.045 per cent. This is far below the acidity of the juice from the isolated entire stomach (as noted above) and is within the range of acidity of the normal gastric content, which Dragstedt and Vaughn (1924) found to be relatively innocuous even to the exposed spleen. By means of a technique modified considerably from that given by Pawlow, we have been able to construct an isolated accessory stomach containing from $\frac{2}{3}$ to $\frac{3}{4}$ of the fundus, leaving only a channel along the lesser curvature not larger in diameter than the duodenum below. Such a large accessory stomach may secrete

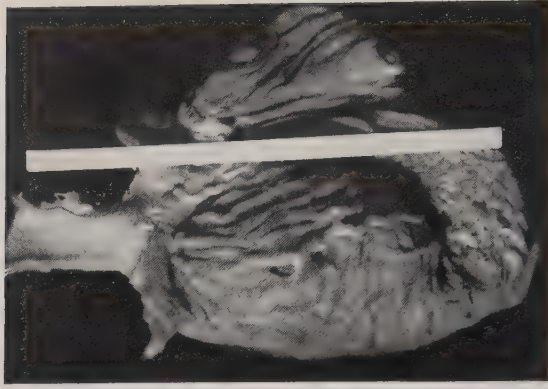


Fig. 11. Photograph showing the formation of a small jejunal ulcer near the suture line and three small gastric ulcers following an operation as in Figure 9. These gastric ulcers are very unusual.

from 800 to 2,800 cubic centimeters of gastric juice in 24 hours with a free acidity ranging between 0.25 and 0.49 per cent (Dragstedt and Ellis, 1930). In one such preparation a large chronic ulcer (see Fig. 6) formed in the Pawlow pouch and ruptured 4 months after the original operation, producing a fatal peritonitis. A striking feature of such a peritonitis which results in the liberation of an exceedingly active secretion into the general peritoneal cavity is illustrated in Figure 7. This extensive widespread digestion of the mesentery and omentum is not seen following the escape of the usual gastric or duodenal content. The occurrence of a chronic progressive ulcer in the isolated accessory stomach and the complete absence of any comparable lesion in the small channel left along the lesser curvature, the gastric canal or *magenstrasse*, is very instructive. The mucous membrane of this literal gastric canal has withstood the mechanical effect of swallowed food and the motility of gastric digestion, and in spite of this the long suture line has healed and remained so. In the accessory stomach, on the other hand, no food has entered and the mechanical effect of coarse food particles massaged into the mucosa by digestion peristalsis has been entirely absent. Nevertheless, an ulcer formed, became chronic and progressive, and finally perforated. The most evident difference between the two portions of the stomach seems to lie in the probable

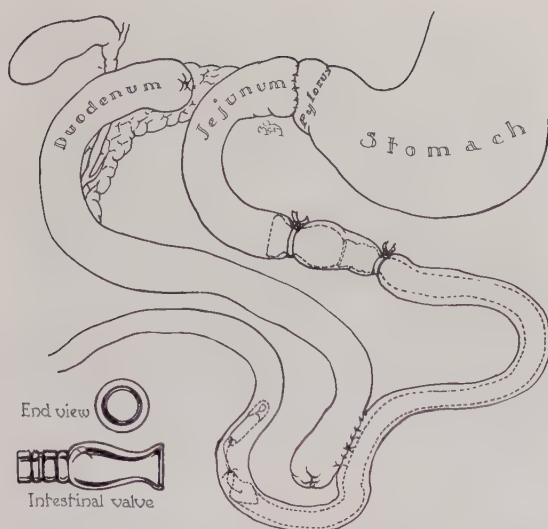


Fig. 12. Diagram illustrating the author's method for producing jejunal ulcers by "surgical duodenal drainage" with high implantation of the duodenum. Regurgitation of duodenal juices in the jejunum is prevented by the valve.

acidity and pepsin concentration of their respective contents. In the one case, the isolated pouch, the free acidity and pepsin concentration was very high while in the other it is probable that its content would fall within the range of acidity and pepsin concentration of the stomach of the normal unoperated animal.

RELATION OF SWALLOWED SALIVA TO THE GENESIS OF GASTRIC ULCER

In the preceding section experimental evidence has been submitted indicating that the pure undiluted gastric juice may, by its chemical action, produce a chronic progressive ulcer in the mucosa of the ileum, jejunum, or stomach. We realize, of course, that only under the highly artificial conditions of these experiments does the mucosa of the alimentary tract become exposed to such pure gastric secretion, and it is our present purpose to inquire into the relative significance of the various factors which operate to reduce the acidity and pepsin concentration to that of the usual gastric content. In this connection it seems clear that the neutralizing effect of swallowed saliva plays at most a very minor rôle. Swanson (1917) demonstrated that removal of the salivary glands does not ap-

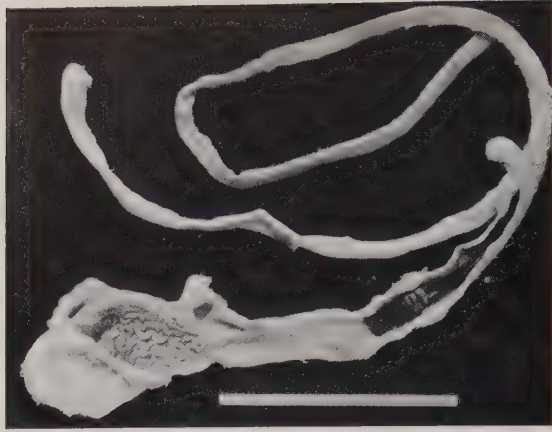


Fig. 13. Photograph showing typical jejunal ulcers in Dog 1, Table II, after operation illustrated in Figure 12. In this case an end-to-side anastomosis was made between the stomach and jejunum.

preciably affect the volume or acidity of gastric secretion from a Pawlow pouch. Since he was interested primarily in the possibility of a hormone from the salivary glands affecting gastric secretion, he made no analyses of the acidity of the contents of the main stomach. No ulcers, however, were found in these animals. We are indebted to Dr. Mary Montgomery for our observations on 3 dogs provided with a total oesophageal fistula in the neck and a gastrostomy. All of the swallowed saliva, of course, escaped by the fistula and the animal was fed with an artificial pabulum administered by way of the opening in the stomach. These dogs were kept in good nutrition for about a year and suffered no ill effects from the loss of saliva. No evidence of ulcer or erosion was found in the stomach or duodenum on postmortem examination.

ABSENCE OF THE NEUTRALIZING EFFECT OF SWALLOWED FOOD IN THE GENESIS OF ULCER

A priori it would appear that the most important single factor in reducing the acidity and pepsin concentration of the secretion of the gastric fundus should be the diluting and neutralizing effect of the food. Most of the proteins are capable of combining with hydrochloric acid and the products of pepsin hydrochloric acid digestion exert an inhibitory effect on the enzyme itself. It is quite probable that a part at least of the favorable

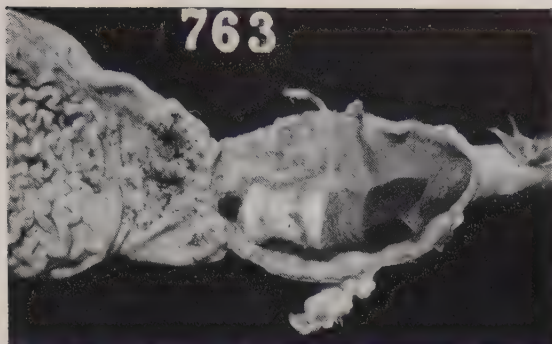


Fig. 14. Photograph showing a chronic perforating jejunal ulcer in Dog 5, Table II, after an operation as illustrated in Figure 12. The valve has been partly withdrawn to show its shape and condition after having been in place 54 days. Its previous location is indicated by the tag of omentum adherent to the intestine about 18 centimeters from the ulcer.

result from the regimen of frequent feeding in the medical management of ulcer is due to this factor. The question is of definite practical importance because from time to time there appears in the literature a suggestion that ulcer patients be treated by duodenal tube feeding or the administration of food by means of a jejunostomy. The idea that such a method puts the stomach at rest is quite false so far as its secretory function is concerned. It has been repeatedly demonstrated in the experimental animal that the introduction of food in the duodenum or jejunum produces a copious secretion of gastric juice. The type of isolated stomach described by Dragstedt and Ellis was found to secrete as much as 2,800 cubic centimeters of gastric juice of high acidity in 24 hours when food passed directly from the œsophagus into the duodenum. Reasoning from this kind of evidence, duodenal tube feeding might be expected to permit the accumulation in the stomach of a gastric content of much higher free acidity than would occur when food is given by mouth, and such a method should be more apt to produce an ulcer in the stomach than to cure one. It is not practicable to feed a dog by duodenal tube, so recourse must be had to other types of experiments which reproduce the desired situation so far as possible.

Silbermann (1927) has reported the occurrence of ulcers in the stomach and duodenum of dogs subjected to repeated "sham feeding"

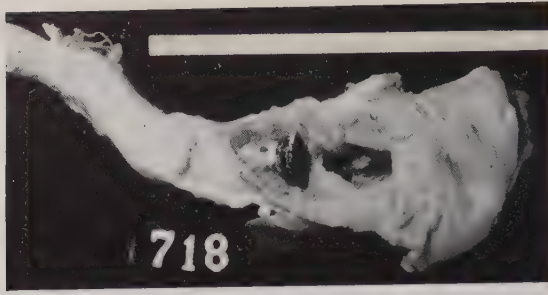


Fig. 15. Photograph showing a large perforating jejunal ulcer in Dog 7, Table II, after an operation as illustrated in Figure 12. The edge of the ulcer is exactly at the line of anastomosis with the stomach. The floor of the ulcer is made up of liver, which is partially eroded.

experiments. A double œsophagostomy was done on 23 dogs and feeding was accomplished through the peripheral œsophageal opening. These dogs were allowed to eat from 40 to 60 minutes three times a day, the swallowed food escaping to the outside via the fistula. Ulcers developed in every case in from 14 to 49 days.

Buechner (1928) reported the occurrence of ulcers in the stomach of rats following the repeated injection of histamine. Buerkle-de la Camp (1929) found that the healing of acute ulcers produced by the injection of silver nitrate beneath the gastric mucosa of dogs was markedly delayed by the repeated injection of histamine. Both the ulcers occurring after sham feeding in dogs and those in rats injected with histamine have been attributed to the secretion of gastric juice in a stomach empty of food. The latter experiments are vitiated somewhat by the discovery of Hoelzel and Da Costa (1931) that ulcers may be produced in the pro-stomach of rats merely by protein restriction, a finding which emphasizes the necessity of adequate nutritional controls in all such work.

We have induced gastric secretion in the empty stomach by two methods but have not to date observed the production of ulcer in the previously intact gastric mucosa. The first observations were made on 3 adult dogs provided with a total œsophageal fistula and a gastrostomy. These animals were in excellent physical condition. When offered food they ate eagerly, but the partially masticated and ensalivated food escaped by way of the œsophageal fistula when swallowed, instead of

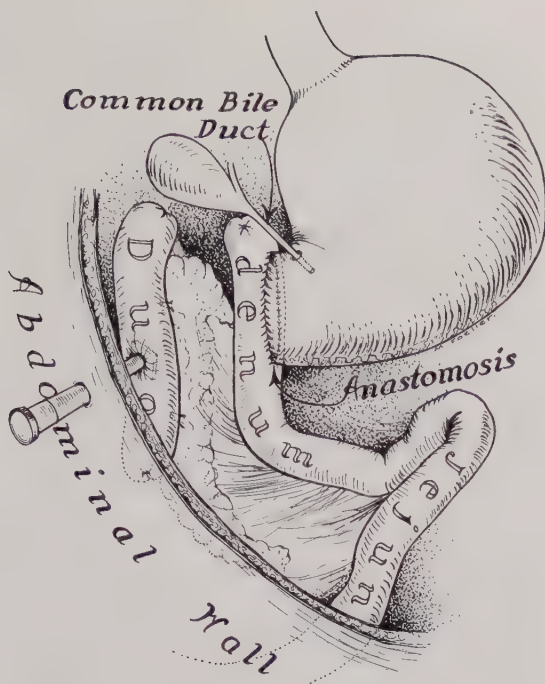


Fig. 16. Diagrammatic illustration of the type of pancreatic fistula used. The pancreatic ducts empty into the isolated closed segment of the upper duodenum and an external fistula has been made of this pancreatic duodenal pouch with a special gold plated cannula.

passing into the stomach. Sham feeding of this type has been shown to produce a copious secretion of gastric juice as a result of reflex stimulation of secretory nerves reaching the stomach in the vagi. All 3 dogs were given such sham meals daily for a period of a month, at the end of which time they were sacrificed and the stomach and duodenum carefully examined. No ulcers were found. These experiments, while decidedly limited in number, suggest that nervous or "appetite" gastric juice does not readily produce a lesion in the empty stomach.

We appreciate of course that this nervous stimulation of gastric secretion is only one phase of the normal mechanism and that perhaps the larger share of the total volume of juice produced is due to the stimulating effect of gastrin bodies elaborated as a result of the presence of food in the stomach or upper intestine. In the following preparation (Fig. 8) we have attempted to provide for the secretion of gastric juice in the empty stomach with



Fig. 17. Photograph showing a large chronic duodenal ulcer in a dog, discovered at autopsy 3 months after the production of a pancreatic fistula as illustrated in Figure 16.

both nervous and "humoral" stimulation and with the normal connections with the duodenum. The stomach was cut across at the cardia, care being used not to injure the vagus nerves supplying the stomach. The upper end of the stomach was infolded and closed. The jejunum was then cut across about 12 inches distal to the duodenojejunal junction, and the lower end of the divided jejunum brought up and anastomosed to the œsophagus. The upper end of the divided jejunum was implanted into the intestine by end-to-side anastomosis about 12 inches from the union with the œsophagus. Such a preparation should provide for a maximum secretion of gastric juice into the stomach empty of food. The presence of food in the mouth with its mastication produces a reflex stimulation of the vagi resulting in the so called appetite secretion and the subsequent entrance of the swallowed food into the upper jejunum provides for the elaboration of gastric secretin and the chemical stimulation of the gastric glands. No food should enter the stomach except as it might overcome the direction of peristalsis in the jejunum. The only factors remaining to reduce the acid pepsin concentration of the fundus secretion are the possible auto-neutralizing effect of gastric mucus or base secreted by the gastric mucosa and the regurgitation of alkaline secretions

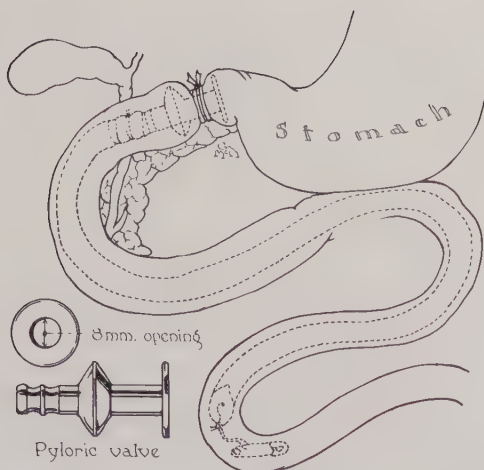


Fig. 18. Diagram illustrating the use of the valve to prevent regurgitation of duodenal juices into the stomach.

from the upper duodenum. We have no direct evidence that either of these factors were actually operative. Only one dog has been studied by this method to date (for 70 days) but in this animal no lesion developed in the stomach, duodenum, or jejunum. Obviously more data are necessary before any final conclusions can be drawn, but the absence of an ulcer in this experiment is in harmony with the evidence detailed in the next section which indicates the great importance of the neutralizing effect of the bile and pancreatic juice.

RELATION OF THE NEUTRALIZING EFFECT OF THE DUODENAL SECRETIONS TO THE GENESIS OF ULCER

Exalto, in 1911, reported that he tied off the pylorus in dogs, performed a gastrojejunostomy, and then drained the duodenal juices of the proximal loop into the cæcum. Jejunal ulcers formed in 6 of 10 animals operated upon in this manner. He discussed his results in the light of the relatively high percentage of jejunal ulcers following the Roux type of gastrojejunostomy, which was popular in part of Europe at that time. The surgical duodenal drainage experiments of Mann and his associates, Williamson, Morton, and McCann, have been especially fruitful in demonstrating the significance of the neutralizing effect of the duodenal secretions in the cause of ulcer. This work has been widely confirmed in this coun-

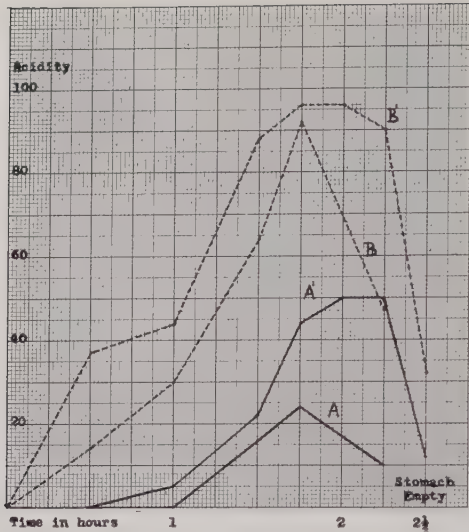


Fig. 19. Curves illustrating the effect of preventing duodenal regurgitation on the acidity of the gastric content after a test meal of meat and water. The uninterrupted lines (A and A') represent free acidity, the broken lines (B and B') total acidity. A and B are pre-operative, A' and B' postoperative curves. Dog 2.

try and later by Weiss and Hubster (1930) in Europe. The experiments discussed below afford further evidence concerning the significance of this neutralization of gastric chyme in the duodenum and also regarding the possible regurgitation of duodenal secretions into the stomach.

In one of the early procedures employed by Mann and his associates (1923) in their study of ulcer, the pylorus was cut across and the duodenal end infolded and closed. The jejunum was then divided just distal to the duodenojejunal flexure, the lower end united to the pyloric end of the stomach by end-to-end suture, and the proximal jejunum implanted into the ileum a short distance above the ileocaecal valve. A very high percentage of animals operated upon in this way developed chronic progressive ulcers in the jejunum a short distance from the line of anastomosis with the stomach. We have confirmed this observation. In repeating the experiment, however, we were impressed by the narrow lumen at the anastomosis and the great thickness of the musculature of the pyloric antrum. Both factors obviously might operate in a mechanical way to produce a

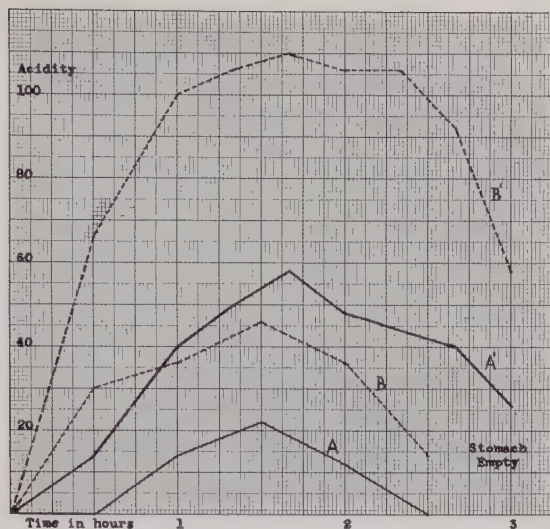


Fig. 20. Curves illustrating the effect of preventing duodenal regurgitation on the acidity of the gastric content after a test meal of meat and water. The uninterrupted lines (A and A') represent free acidity, the broken lines (B and B') total acidity. A and B are pre-operative, A' and B' postoperative curves. Dog. 3.

mucosal lesion and prevent its healing. Mann himself recognized this point and believed that the motor drive of the stomach and the direction of the stream of gastric chyme were important in determining the site of the resulting ulcer. The following modification of Mann's experiment was devised to test the importance of these factors. Five dogs were operated upon as described except that the muscular pyloric antrum was first resected and a wide anastomosis made between the large open end of the stomach and the side of the jejunum (Fig. 9). A gastric outlet of this nature should not permit a narrow stream of acid chyme to be forcibly ejected against a single area of jejunal mucosa. However, in every case (100 per cent) jejunal ulcers developed (see Figs. 10 and 11). These ulcers were small and shallow and located at the lower end of the gastro-jejuno-stomy, i.e., opposite the greater curvature of the stomach. They were not so deep or extensive as the ulcers following the end-to-end gastrojejuno-stomy, possibly because the "motor drive" effect was dissipated. These experiments were completed before the similar work of Ivy and Fauley (1931) was published and confirm their findings. These investiga-

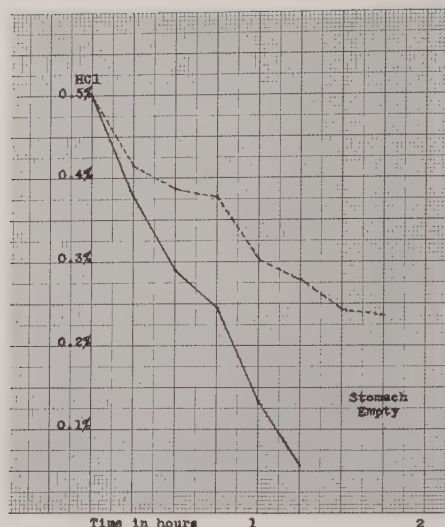


Fig. 21. Curves showing the neutralization of 200 cubic centimeters 0.5 per cent hydrochloric acid placed into the empty stomach before and after the introduction of the pyloric valve to prevent duodenal regurgitation. The broken line represents the postoperative results. Bile was present in the pre-operative aspirations consistently after the first $\frac{1}{2}$ to 1 hour, but never after the valve was put in. Dog. 12.

tors reported that of 11 dogs operated upon in this manner, 5 developed jejunal ulcers. We may probably correctly infer then that the jejunal ulcers developing in this type of experiment are not dependent upon the "nozzle-like" effect of a narrowed pyloric orifice. We cannot, however, conclude from these experiments that the removal of a local neutralizing solution is the sole pathogenic factor in the ulcer formation. Both the animals operated upon by the exact technique of Mann and by our modified method developed a rapid and progressive cachexia. Immediately after the operation, all the dogs began to display a profuse watery diarrhoea which improved somewhat after a few days. The diarrhoea was usually accompanied by some loss of appetite. The weight loss was marked and progressive, and many animals lost 50 per cent of their original body weight in 1 to 2 months. They all died within 2 months in spite of freedom from laboratory infections. It seems likely that death was caused by the nutritional disturbance rather than the jejunal ulcers, most of which did not perforate nor cause excessive hæmorrhage. The factors in this nutritional

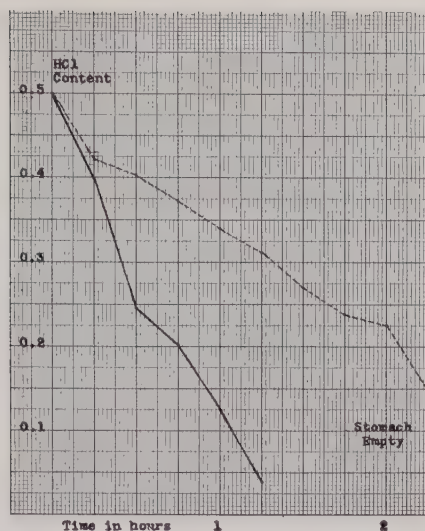


Fig. 22. Curves showing the neutralization of 200 cubic centimeters 0.5 per cent hydrochloric acid placed into the empty stomach before and after the introduction of the pyloric valve to prevent duodenal regurgitation. The broken line represents the postoperative results. Bile was present in the pre-operative aspirations consistently after the first $\frac{1}{2}$ to 1 hour, but never after the valve was put in. Dog. 13.

disturbance are probably two-fold. The absence of two very important digestive secretions from the upper absorptive small intestine might be expected to interfere markedly with the digestion and absorption of food; and, second, the partial failure of reabsorption of pancreatic juice and bile, because of the low implantation, might be expected to result in dehydration and excessive loss of electrolytes from the blood and body fluids (Elman and McCaughan, Dragstedt, Montgomery, Matthews and Ellis). It is well recognized that cachexia produced by repeated hæmorrhage or infections (Ivy, 1920) or food deficiencies (Hoelzel, etc.) may operate to delay the healing of gastric lesions or induce ulcers. The cachexia is controlled by drainage of the duodenum higher into the jejunum, but under these conditions ulcers do not develop in the jejunum or the stomach. This failure of ulcer formation when the duodenum is implanted into the middle or upper jejunum has been attributed by Mann to a possible regurgitation of the duodenal secretions back orally through the jejunum and neutralization of the acid chyme in the region of the gastro-

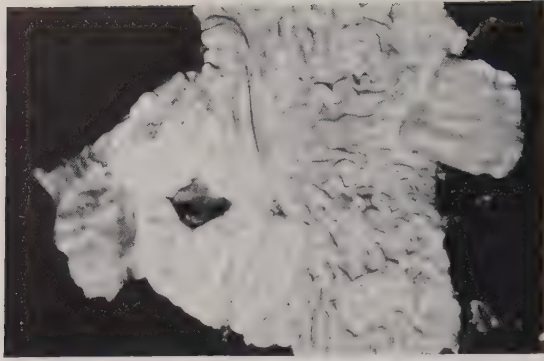


Fig. 23. Photograph showing an acute gastric ulcer in a control animal 72 hours after the injection of 1.5 cubic centimeters of 5 per cent silver nitrate.

jejunostomy. This interpretation seemed rather improbable to us and the following experiments were devised to test its validity. The results indicate that it is probably correct and in addition furnish further controls with regard to the significance of operative trauma in the genesis of these "duodenal drainage jejunal ulcers."

Healthy adult dogs were secured and all operations were performed under complete ether anæsthesia and with the usual aseptic precautions. The procedure is illustrated in Figure 12. The pylorus was divided and the duodenum infolded and closed. The jejunum was then cut across just below the ligament of Treitz and the distal jejunum united to the pyloric end of the stomach by end-to-end suture. The distal end of the duodenum was implanted into the jejunum about 40 centimeters from the anastomosis with the stomach. No clamps were used in the operation. No. 00 chromic catgut was used for suture material and great care was taken not to injure the blood supply to the region of anastomosis. The animals promptly recovered from this somewhat extensive operation and remained in good condition thereafter. After a period of from 80 to 300 days, a second laparotomy was done and the region of the anastomosis between the jejunum and stomach carefully examined. In only 1 of the 21 dogs operated upon in this manner was a jejunal ulcer found, a striking contrast to the high incidence of such ulcers when the duodenal juices were drained into the lower



Fig. 24. Photograph showing a chronic gastric ulcer in Dog 6, 30 days after the injection of silver nitrate, where duodenal regurgitation has been prevented by a valve in the pylorus.

ileum. To determine if this freedom from ulcer formation was due to the regurgitation of alkaline pancreatic juice and bile to the region of the gastrojejunostomy, a specially devised valve was then introduced into the segment of jejunum between the two anastomoses (see Fig. 12). This valve was so constructed as to permit of the flow of intestinal content only in one direction and so effectually prevented any regurgitation. The valve consisted essentially of an aluminum ring to which was attached a long piece (40 centimeters) of easily collapsible rubber tubing (Penrose). The ring was held in place in the jejunum by means of two tapes encircling the bowel, one being placed around the ring and one just below it. The inside diameter of the ring varied from 0.9 to 1.2 centimeters which was found adequate to prevent obstruction in most instances. Following the introduction of the valve at this second operation, the diet was restricted to finely divided and liquid foods. The postoperative course varied somewhat. Five of the animals died of peritonitis due to a transection of the jejunum because of too tight a ligature about the aluminum ring. In six the ligatures were too loose, and the valve was passed with the feces. Ten of the animals retained the valves and of these 6 developed progressive ulcers in the jejunum. The data are summarized in Table II.

The photographs in Figures 13, 14, and 15 illustrate quite well the large size of these ulcers and their characteristic punched-out

TABLE II.—INCIDENCE OF JEJUNAL ULCER
AFTER THE OPERATION ILLUSTRATED IN
FIGURE 12.

Dog No.	Time between first and second operations	No. days after second operation when death occurred	Autopsy findings
1	None*	61	Chronic ulcer 2 cm. in diameter. Small perforation
2	170 days	63	No ulcer
3	173 days	42	No ulcer; dog died of hæmorrhage from erosion by valve into intestinal wall
4	97 days	157	Chronic ulcer, 1.5 cm. in diameter and 0.3 cm. deep. Perforated
5	96 days	54	Chronic ulcer, 1 cm. x 0.6 cm. Perforated
6	88 days	12	Acute ulcer, 0.4 cm. in diameter. Perforated
7	87 days	65	Chronic ulcer, very large and deep. Base made of liver. Perforated
8	101 days	46	No ulcer. Animal died of obstruction of valve by hairball
9	77 days	16	No ulcer. Animal died of obstruction of valve by hairball
10	70 days	81	Chronic ulcer, 2 x 1 cm. Perforated

*In Dog 1 all the operative work was done in one stage.

margins. It is significant that in each case the ulcer developed near the anastomosis with the stomach and at some distance from the valve. It is accordingly improbable that the valve exerted any local irritating effect of consequence in the genesis of the lesion. There was always a considerable inflammatory reaction around the valve. Numerous adhesions were present and the omentum was greatly thickened where it had been wrapped around the jejunum. The dogs remained in good physical condition following the second operation except those that died accidentally, as noted in Table II (i.e. Dogs 3, 8, 9). Each of the dogs (Dogs 2, 3, 8, and 9) which did not develop ulcer died from an accidental cause. It is possible that the incidence of ulcer formation might have been higher had it been possible to keep all the animals alive under the conditions of the experiment.

The data obtained in these experiments are instructive in that they rule out cachexia and surgical trauma as important factors in the genesis of the jejunal ulcer of the Mann experiment. The high implantation of the duodenal loop caused much less disturbance

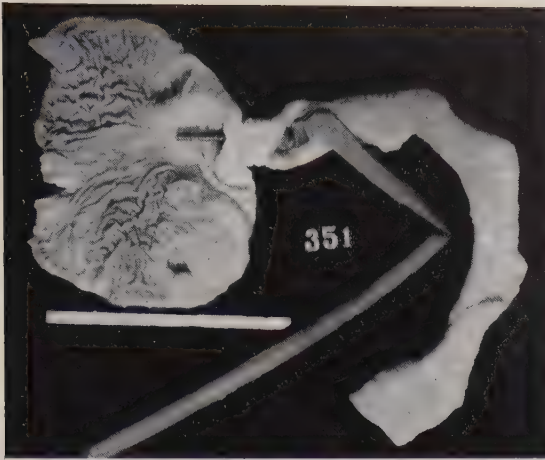


Fig. 25. Photograph showing a chronic ulcer in a transplant of duodenum in the gastric wall where duodenal regurgitation has been prevented by a valve in the pylorus. The metal screw was placed inside the valve to indicate its position and the duodenum has been slit open to show the rubber tubing.

in digestion and absorption than when the bile and pancreatic juice passed into the lower ileum. The long interval between the first operation and the introduction of the valve permitted the anastomosis between the stomach and duodenum to become well healed and demonstrated that the trauma of operation and the mechanical factors of digestion operating were insufficient to produce a jejunal ulcer. The development of such an ulcer in a relatively high percentage of cases after the introduction of the valve, which so far as we can see acts only to prevent a regurgitation of the alkaline duodenal juices, is to our mind very strong evidence that this failure of neutralization of the acid gastric chyme is the factor of prime importance in such ulcer formation. The efficiency of the valves in preventing regurgitation of intestinal content is indicated by the following evidence. After the first operation, consisting of a gastro-jejunoscopy with high implantation of the duodenal loop, bile was frequently found in the gastric content but never after the introduction of the valve. Curiously enough, however, the acidity of the gastric content as determined by test meals was but little affected by the valve. At autopsy the jejunal mucosa above the valve was never bile-stained and water introduced into the intestine below the

valve could not be forced by it into the upper jejunum.

OCCURRENCE OF CHRONIC PROGRESSIVE DUODENAL ULCER IN DOGS WITH PANCREATIC FISTULÆ

In 1930 Dragstedt, Montgomery, and Ellis described a new method for the construction of a permanent total pancreatic fistula in the dog. The upper portion of the duodenum, into which the various pancreatic ducts empty, was converted into a closed sac and connected to the exterior by means of a special gold plated cannula. The common bile duct was then implanted into the stomach and the continuity of the alimentary tract re-established as indicated in the diagram in Figure 16. The dogs readily recover from this somewhat extensive operation, and if care is taken to replace the minerals lost in the pancreatic juice by the daily intravenous administration of salt solution, they may be kept in fairly good nutrition in the laboratory for long periods. We have prepared a number of such animals in connection with other work. They all developed one, or more, very large chronic ulcers in the duodenum near the anastomosis with the stomach (Fig. 17). Several of these caused death from hæmorrhage or perforation. These observations confirm the findings of Elman (1931).

It is significant that we have been able to prevent this ulcer formation for periods as long as 6 months by the oral administration of calcium carbonate, sodium bicarbonate, or finely ground bone meal. In one such animal preserved in good nutrition for 5 months by this neutralization therapy, an acute ulcer developed in the duodenum and caused a fatal hæmorrhage 3 days after the therapy was stopped.

EFFECT OF THE PREVENTION OF DUODENAL REGURGITATION INTO THE STOMACH

The suggestion that the acidity of the fundus secretion of the stomach was under normal conditions partially neutralized by the regurgitation of duodenal secretions, was first elaborated by Boldyreff about 30 years ago. He claimed that such a regurgitation invariably occurred when the acidity of the stomach

content approached that of pure gastric juice. For example, 200 cubic centimeters of 0.5 per cent hydrochloric acid placed in the empty stomach of the dog and removed 1 hour later was found to have an acidity of only 0.2 to 0.15 per cent and to contain both bile and pancreatic enzymes. If the pancreatic ducts were previously ligated or the pancreatic juice removed by means of a fistula, the neutralization proceeded so slowly that little change was noted even after several hours. Pancreatic juice was considered more effective in this neutralization than the other duodenal secretions combined. Elman has recently confirmed and extended these findings of Boldyreff and has in addition reported the following highly significant observation. Three hundred cubic centimeters of 0.5 per cent hydrochloric acid introduced into the empty stomach of a patient suffering from an ulcer near the pylorus was much more slowly neutralized than in the normal human stomach. This he attributed to decreased duodenal regurgitation because of pylorospasm. A number of observers have noted the infrequent appearance of bile in the gastric content of patients with pyloric ulcer as compared with the normal.

The development of a valve similar to the one described in the preceding section which permits the passage of intestinal content in only one direction has made it possible for us to study the effect of preventing duodenal regurgitation on the acidity of the gastric content, on the healing of artificial wounds in the gastric mucosa, and on the production of ulcers in implants of intestinal mucosa in the gastric wall. For this work short tubes of gold-plated brass or aluminum were used, to one end of which a piece of thin walled collapsible rubber tubing (Penrose) about 40 centimeters in length was attached. The valve was placed in the pylorus as indicated in Figure 18, the rubber tubing extending into the lower duodenum. A heavy linen ligature placed about the pylorus was found sufficient to hold the valve in place. After some experimentation it was found that valves with an inside diameter of 8 millimeters were large enough to permit of normal emptying of the stomach.

Healthy adult dogs of average size (10 to 14

kilograms) were selected and all operations were performed under complete ether anaesthesia and with the usual aseptic precautions. An incision was made in the anterior wall of the stomach about 10 centimeters from the pylorus and the valve fixed in place as indicated above. At the same time an acute ulcer was produced on the posterior wall of the stomach by injecting 1.5 cubic centimeters of 5 per cent solution of silver nitrate just beneath the mucosa. The gastrotomy wound was closed with catgut. Intravenous fluids were given for 3 or 4 days after the operation and thereafter only liquids and finely divided food by mouth in order to prevent obstruction through possible clogging of the valve. Repeated gastric analyses were made both before and at varying periods after the operation.

a. *Effect of preventing duodenal regurgitation on the acidity of the gastric content.* For this determination a test meal similar to the one described by McCann (1929) was employed. The animals were given no food for 24 hours before the examination and the stomach was then proved to be empty by lavage and aspiration. A meal of 80 grams of finely ground, raw, lean beef, and 250 cubic centimeters of water were given and fractions secured by aspiration every 20 to 30 minutes until the stomach was empty. The curves in Figures 19 and 20 taken from 2 typical experiments prove that the prevention of duodenal regurgitation has raised both the free and total acidity of the gastric content. It will be noted that not only are the free and total acidity higher after the operation than before, but the height of the acidity is sustained longer than before operation. Occasionally in a pre-operative fractional analysis, one sample of gastric content in a series might show an unusually high free acidity. In several such cases the succeeding sample was slightly bile colored and of decidedly lower acidity. In these experiments before operation bile was usually not present except toward the end of the experiment. In no case was bile found in the stomach after the introduction of the valve.

b. *Effect of preventing duodenal regurgitation on the neutralization of acid introduced into the stomach.* In these experiments no food was

given for 24 hours and the stomach proved to be empty by lavage and aspiration as before. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid was then placed in the stomach and fractions removed every 15 minutes for examination until the stomach was empty. The curves in Figures 21 and 22 taken from two representative experiments indicate that the acid introduced into the stomach is rapidly neutralized in part at least in the normal animal but only much more slowly in the same animal after duodenal regurgitation has been prevented. These findings confirm the observations of Boldyreff many years ago.

c. *Effect of preventing duodenal regurgitation on the emptying time of the stomach.* The emptying time of the stomach was determined by a method similar to the one described by Ivy and Fauley (1929). Twenty-four hours after the last feeding the stomach was proved to be empty by lavage and aspiration. A meal consisting of 80 grams of ground lean beef, 40 grams of white bread, 60 grams of barium sulphate, and 300 cubic centimeters of water, mixed together to form a thick paste, was then given and eaten readily. Fluoroscopic examination was made immediately and thereafter every 30 minutes until the stomach was empty. The examinations were made with the dogs lying back down and held in position by a frame especially devised for this purpose. Both the gastric analyses and the emptying time tests were repeated many times on the same animal until the results became consistent. Several weeks were usually required for training. At first the animals were frightened and struggled somewhat but in a short time became gentle and even co-operative, apparently little disturbed by the experiments. During the early period 6 to 8 hours were frequently required before the stomach became empty whereas, after training, the same animal emptied the stomach quite regularly in 4 to 4½ hours. For 2 weeks after the introduction of the valve in the pylorus the emptying time was prolonged to 12 hours or more. After this time, however, the stomach seemed to become adapted to the presence of the foreign body and the emptying time ranged between 4½ and 5½ hours, or only slightly more than before operation. It

is probable that the valves produced an actual slight pyloric stenosis, since the gastric peristalsis was noticeably more vigorous than before operation. The ulcers (see below) were not detected by fluoroscopic examination.

d. *Effect of preventing duodenal regurgitation on the healing of acute gastric ulcers.* After control observations had been made on the gastric response to a test meal and to the Boldyreff acid meal as already described, the animals in this series were operated upon and the special valve placed in the pylorus. At the same time an acute ulcer was produced on the posterior wall of the stomach by injecting 1.5 cubic centimeters of 5 per cent silver nitrate beneath the mucosa. Control animals were injected in a similar way with the same amount of silver nitrate. The injection produced an immediate local necrosis, the slough being digested away in about 48 hours, leaving a sharply circumscribed superficial ulcer (Fig. 23). In the control animals these acute lesions invariably healed in 15 to 18 days, a confirmation of the observations of Friedman and Hamburger (1914) and L. R. Dragstedt (1917). In 13 animals in which duodenal regurgitation was prevented by the valve, healing of the acute lesion was delayed in 6 cases. The data are summarized in Table III. Three of the animals were sacrificed after 25, 26, and 32 days, respectively, and of these one ulcer was still present (25 days), the others being healed. Six animals were sacrificed after 30 days, and, in these, 3 ulcers were still present (Dogs 5, 6, and 9), the remainder being healed. Four were examined after 45 days. Of these 2 ulcers were still present and 2 were healed. Had it been practicable to examine these lesions at shorter intervals after operation, a more detailed account might be given of their rate of healing. All of the ulcers showed signs of healing except one, which was examined after 30 days and which seemed to have become chronic and progressive (Fig. 24). It had a thickened indurated base and the gastric content at postmortem examination was dark brown and contained blood. The remaining ulcers were shallow, not thickened, and a narrow rim of regenerating gastric mucosa could be seen around the border of each. Histologically,

TABLE III.—EFFECT OF PREVENTING REGURGITATION ON HEALING

Summary of the data indicating the effect of preventing duodenal regurgitation on the healing of acute lesions in the stomach

Dog No.	Length of experiment days	Condition of ulcer
1	32	Healed
2	26	Healed
3	25	Unhealed but healing; 1.4 x 1.0 cm.
4	30	Healed
5	30	Unhealed, healing; 1.0 cm. in diameter
6	30	Chronic ulcer; 1.5 cm. in diameter
7	30	Healed
8	30	Healed
9	30	Unhealed but healing; 0.8 cm. in diameter
10	45	Healed
11	45	Unhealed but healing; 0.4 cm. in diameter
12	45	Healed
13	45	Unhealed but healing; 0.4 cm. in diameter

these healing ulcers did not present any signs of inflammation and the surrounding mucosa appeared normal.

e. *Effect of preventing duodenal regurgitation on the development of ulcers in intestinal transplants in the stomach.* The experiments of L. R. Dragstedt and Vaughn (1924), in which transplants of sections of intestine, of spleen, and kidney, into the stomach wall were found to be very little affected by the gastric content, have been referred to above. However, in view of the delayed healing of gastric wounds and the increase in gastric acidity when duodenal regurgitation is prevented as described in the preceding section, it seemed desirable to determine whether transplants of intestinal patches into the stomach would survive under the same conditions. Morton (1928) has attacked this problem in a slightly different manner but in general our results confirm his findings. He transplanted sections of intestine into the stomach of dogs otherwise normal and found that these persisted, the mucosa remaining unchanged. When he

TABLE IV.—EFFECT OF PREVENTING REGURGITATION IN TRANSPLANTS

Summary of the data with regard to the incidence of ulcers in intestinal transplants in the gastric wall where duodenal regurgitation has been prevented by a valve in the pylorus

Dog No.	Length of experiment days	Source of patch	Condition of patch
10	45	Duodenum	Two chronic ulcers 2.2 cm. diameter and 1.0 x 0.6 cm.
4	30	Duodenum	Two chronic ulcers 1 cm. diameter
11	45	Jejunum	No ulcer
5	30	Jejunum	No ulcer
12	45	Ileum	Large chronic ulcer 5 x 1 cm.
6	30	Ileum	No ulcer
13	45	Colon	No ulcer
7	30	Colon	Two chronic ulcers 3 x 5 cm. and 2 x 4 cm.

drained the duodenal juices into the lower ileum as in the Mann-Williamson technique, 3 of the 13 animals developed chronic ulcers in the transplants.

In our experiments transplants of intestinal mucosa into large gastric defects were made, as described by the above investigators. Great care was observed not to injure the blood supply to the transplant and only catgut was used for suture material. Sixteen dogs in all were operated upon, and in 4 transplants were taken from the duodenum, 4 from the jejunum, 4 from the ileum, and 4 from the colon. The operations produced little or no subsequent ill effects. However, several of the animals developed severe respiratory infections and it is interesting that of these 2 showed evidence of ulceration in the intestinal transplant (one a colon and the other a jejunal patch) when examined a month later. In all of the others the intestinal transplants were normal, examination being made through a gastrotomy opening at a second operation.

In 8 of the animals, which seemed in the best physical condition, a pyloric valve was introduced at the second operation, the remaining 8 being kept for control. They were then returned to their cages and the post-

operative course carefully observed. It was decided to terminate the experiment short of 50 days since in our experience the pyloric valves can only rarely be made to remain in place for a longer period. Half of the animals were sacrificed 30, and half, 45 days after the second operation and postmortem examinations were made immediately. With the exception of the 2 animals already noted, both of whom had severe respiratory infections, the transplants in the control group persisted and the mucosa remained normal. The data with regard to the transplants in the stomach where duodenal regurgitation was prevented by the pyloric valve are summarized in Table IV. It will be noted that 4 of the 8 developed ulcers in the intestinal transplants and of these 2 occurred in the duodenal mucosa. One of these is illustrated in Figure 25.

SUMMARY

1. Experimental reproduction in the lower animal of a counterpart of the Meckel's diverticulum ulcer of man, by the implantation of a small isolated pouch of gastric wall into the jejunum and ileum, yielded chronic progressive ulcers in 85 per cent of trials in the former and in 100 per cent in the latter. This is a striking example of the susceptibility of an organism's living tissues to the irritant action of its own pure, active gastric juice.

2. A chronic progressive ulcer developed in a totally isolated stomach, in the entire absence of food or the motility of digestion, and where the important exciting factor was probably the high acid pepsin concentration of the pure gastric secretion.

3. A chronic progressive ulcer developed in the wall of a large Pawlow accessory stomach, which took no part in digestion, whereas the remainder of the stomach, consisting of a small tube made up of the lesser curvature (*magenstrasse* or gastric canal) and upon which the entire burden of gastric digestion depended, remained entirely normal.

4. The development of jejunal ulcers after surgical duodenal drainage as in the experiments of F. C. Mann and his associates is probably not due to mechanical factors or motility, since they occurred in 100 per cent

of such animals where the muscular pyloric antrum was first resected and a very wide anastomosis made with the jejunum.

5. A repetition of the experiment of gastro-jejunosomy and surgical duodenal drainage, as in the Mann experiment, but with implantation of the duodenum 40 centimeters below the anastomosis of the jejunum with the stomach, resulted in the development of only 1 ulcer in 21 experiments. This freedom of ulcer formation was due to the regurgitation of duodenal juices to the region of anastomosis, since the introduction of a valve to prevent such regurgitation led to the formation of chronic progressive jejunal ulcers in 6 cases.

6. Preventing the regurgitation of alkaline duodenal juices into the stomach of normal dogs, by fixing a valve in the pylorus, raised both the free and total acidity of the gastric content after a standard test meal, delayed the neutralization of 0.5 per cent hydrochloric acid placed in the stomach, delayed the healing of acute ulcers in the gastric mucosa produced by the injection of silver nitrate, and caused the appearance of spontaneous ulcers in transplants of intestinal mucosa sutured into defects in the stomach wall.

7. The experimental evidence presented in this paper has been interpreted by the author to afford substantial support to the view that the chemical action of pepsin hydrochloric acid (of the concentration found in pure gastric juice) can by itself alone produce a typical chronic progressive ulcer in the stomach, duodenum, jejunum, ileum, or colon. The resistance of these organs to the digestive action of pure gastric juice decreases progressively from the stomach to the colon. In the application of these findings to the problem of spontaneous ulcer in man, it should be emphasized that no evidence has been offered which contradicts the possible deterrent action of gastric motility and the mechanical action of coarse food in the healing of acute lesions of the stomach or duodenum. Of these three factors operative in healthy individuals, however, the chemical action of the gastric secretion seems to be the most important both in the production of the acute lesion and in its subsequent chronicity.

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